High-Throughput Manufacturing Methods for Engineered MRI Contrast Agents

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Description:

Microfabricated magnetic imaging agents with greater sensitivity and new functionality for magnetic resonance imaging (MRI) have recently been demonstrated at NIST [1-4]. The technology relies on thin-film fabrication methods adapted from the semiconductor industry. This “top-down” approach is expensive and suffers from low yield compared to “bottom-up” methods based on chemical synthesis for making other types of contrast agents. NIST seeks applications focused on the development and demonstration of high-throughput techniques for making this new class of MRI contrast agent in sufficient quantity that biologists and physicians can explore new applications. These methods must achieve the necessary control of dimensional and materials properties at nanometer size scales. In addition, manufacturing methods must lead to materials that can be readily prepared for animal studies and potentially for clinical trials using methods currently available in the biomedical community.

The technical proposal must provide details on how to achieve the following goals:

1. Manufacturing methods will lead to contrast agents with the sensitivity and functionality similar to those demonstrated at NIST using wafer-based manufacturing methods. For T2* agents (see Ref. [1]) , this implies micrometer-scale magnetic particles with sizes and magnetic moments that vary by no

more than 5 to 10 % (ideally less) from one particle to another. For multispectral agents (see Refs. [2-4]), this implies, in addition, that magnetic particle shapes are sufficiently well controlled and similar to one another to ensure that the resulting shifted nuclear magnetic resonance (NMR) water linewidths generated by single particles, as well as by ensembles of particles, are no more than 10 to 20 % (ideally less) of the NMR frequency shift itself. For example, methods for making hollow magnetic nano-cylinders [3] should ideally have control to within a few percent over the thickness of the cylinder wall as well as the length and diameter of the cylinder. Depending on cylinder size, this may translate to control of a few nanometers for wall thickness and of a few tens of nanometers for cylinder length.

2. Manufacturing methods should be capable of producing millimolar solutions in 0.1 liter batches for in-vivo biological applications.

3. Manufacturing methods should have promise for producing contrast agents at a cost that is comparable with that of current imaging agents for MRI.

NIST seeks applications that address the issues identified above, as well as methods that streamline wafer based manufacturing (such as nano-imprinting), use roll-to-roll transfer techniques, use chemical synthesis approaches, or a combination of any of the above.

Phase I activities and expected results:
Demonstrate a manufacturing method for producing contrast agents that have sensitivity and functionality similar to those of microfabricated contrast agents that have been produced at NIST using wafer-based manufacturing methods.

Phase II activities and expected results:
Show the capability for producing millimolar solutions of sufficient quantities at a cost that is comparable to that of current MRI contrast agents.

NIST will be available for consultation and collaboration, including testing contrast agents for sensitivity and functionality.

References:

1. G. Zabow, S.J. Dodd, E. Shapiro, J. Moreland, A.P. Koretsky, *Microfabricated High-Moment Micrometer-Sized MRI Contrast Agents*, MAGNETIC RESONANCE IN MEDICINE 65, 645–655. (2011).

2. G. Zabow, S.J. Dodd, A.P. Koretsky, *Ellipsoidal Microcavities: Electromagnetic Properties, Fabrication, and Use as Multispectral MRI Agents*, SMALL 10, 1902–1907. (2014).

3. G. Zabow, S.J. Dodd, J. Moreland, A.P. Koretsky, *The Fabrication of Uniform Cylindrical Nanoshells and their Use as Spectrally Tunable MRI Contrast Agents*, NANOTECHNOLOGY 20, 385301. (2009).

4. G. Zabow, S.J. Dodd, J. Moreland, A.P. Koretsky, *Micro-Engineered Local Field Control for High-Sensitivity Multispectral MRI*, NATURE 453, 1058–1062. (2008).